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INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer in North American men and it is estimated that there are over 300,000 newly diagnosed cases each year (1, 2). The incidence and mortality rates from prostate cancer are increasing and this is due, in part, to an increasingly aging population and the higher incidence of this disease in older men (3, 4). Prostate cancer therapy is dependent on the stage of the tumor and AR expression. Early stage androgen-responsive prostate cancers can be treated by castration or with antiandrogens or drugs that block androgen-induced responses including steroidal antiandrogens (cyproterone), LHRH analogs, nonsteroidal antiandrogens (flutamide, nilutamide, bicalutamide), and the potent estrogenic drug diethylstilbestrol (reviewed in 5-8). In addition, there are several novel strategies for treatment of prostate cancer and other tumor-types and these include targeting of critical genes involved in tumor cell growth and metastasis (e.g. antiangiogenic drugs, antisense therapy) (9-13). Ligands for nuclear receptors (NR) are also being developed for treatment of prostate cancer through inhibitory NR-AR crosstalk that involves various compounds that bind the retinoid acid/X-receptors (retinoids), vitamin D receptor (calcitrol), and peroxisome proliferator activate receptor γ (troglitazone) (14-26). A recent study in androgen-responsive LNCaP prostate cancer cells showed that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a ligand for the aryl hydrocarbon receptor (AhR), inhibited testosterone-induced cell proliferation and gene/reporter gene expression (27). We have developed a series of alternate-substituted (2,3,6,8- and 2,4,6,8-) alkyl polychlorinated dibenzofurans (PCDFs) and substituted diindolymethanes (DIMs) (Fig. 1) that inhibit rodent mammary tumor growth *in vivo*, but do not induce toxic responses

associated with exposures to TCDD (28-35). These selective AhR modulators (SAhRMs) are therefore an important new class of drugs that target the AhR and they have been successfully used for inhibiting growth of breast tumors/cells (28-35) and pancreatic cancer cells (36). Studies sponsored by this grant are focused on inhibitory AhR-AR crosstalk in human prostate cancer cells and applications of SAhRMs for treatment of this disease. These studies will include characterization of the Ah-responsiveness of several prostate cancer cells, inhibition of prostate cancer cell growth by SAhRMs, mechanisms of inhibitory AhR-AR crosstalk and *in vivo* inhibition of prostate tumor growth by SAhRMs in athymic nude mice bearing prostate cancer cell xenografts.

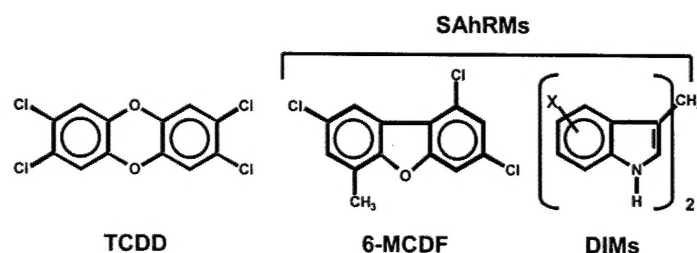


Figure 1. TCDD and selective AhR modulators (SAhRMs) 6-MCDF and DIM.

BODY

Characterization of Ah-responsiveness of prostate cancer cells

The first part of this project (Task 1) has been focusing on characterization of Ah-responsiveness of several prostate cancer cell lines by determining induction of CYP1A1-dependent activities by TCDD and by SAhRMs. The results in Figure 2 summarize the concentration-dependent induction of ethoxyresorufin O-deethylase (EROD) activity by TCDD (note: this activity is catalyzed by CYP1A1). TCDD clearly

induces EROD activity in 22RV1 prostate cancer cells at concentrations of 0.1, 1.0 and 10.0 nM (Fig. 2A); the EC_{50} value is < 0.1 nM and a > 14 -fold induction response was observed. In a parallel experiment, DIM exhibited minimal induction of EROD activity (Fig. 2B), and this is consistent with previous reports showing that DIM is a weak AhR agonist/partial antagonist for this response.

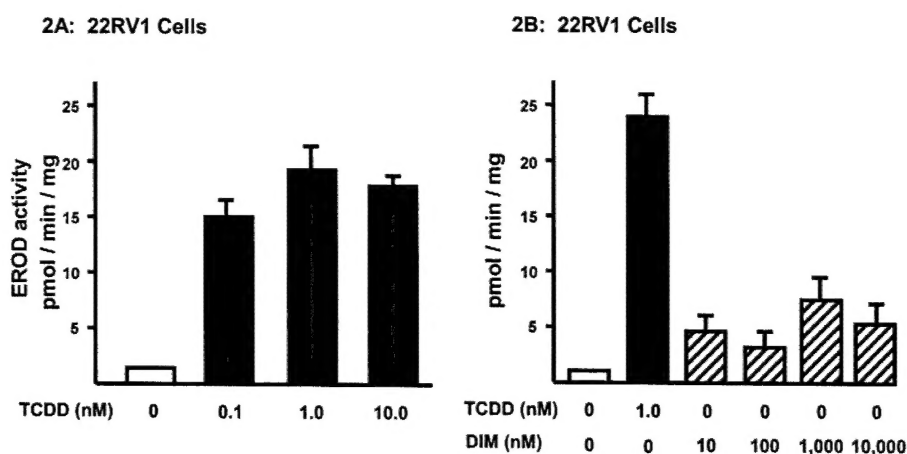


Figure 2. Induction of CYP1A1-dependent EROD activity by DIM and TCDD in 22RV1 prostate cancer cells.

The induction of EROD activity by TCDD and DIM in PC3 prostate cancer cells was also investigated using serum-free medium. The results after treatment for 24 h showed that 10 nM TCDD and both 1 and 10 μ M DIM induced EROD activity (< 3 -fold) (Fig. 3). In contrast, 1 nM TCDD was not active. The experiments were therefore extended for 48, 72 and 96 h, and the results showed the novel effects of prolonged treatment with TCDD or DIM on induction of EROD activity. The lower concentrations of TCDD (1 nM) and DIM (1 μ M) were not inducers at the longer time periods, and the induction response by 10 μ M DIM was similar at all time points. In contrast, prolonged treatment with 10 nM TCDD increased induction of EROD activity and after 96 h, there

was a > 29-fold induction response. These results demonstrate that the AhR is functional in PC3 prostate cancer cells; however, optimal responsiveness is observed only after 96 h and the reason for this unusual temporal pattern of Ah-responsiveness is currently being investigated. Previous studies have demonstrated that LNCaP prostate cancer cells are also Ah-responsive, and this was also observed in our studies which show that TCDD induced luciferase activity in cells transfected with a construct containing three tandem dioxin response elements linked to a luciferase reporter gene (pDRE₃) (data not shown).

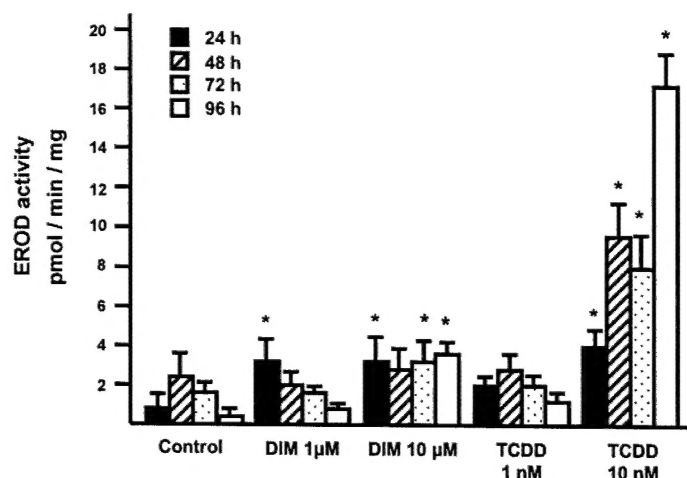


Figure 3. Induction of EROD activity by DIM and TCDD in PC3 prostate cancer cells. Cells were seeded 50,000 per well in 48-well plates in DME + 5% stripped serum and allowed to attach 24 h. Cells were then treated with DMSO vehicle or treatments in DMSO one time in DME-F12 media without serum supplementation, with 7 or 8 wells per treatment group. On separate plates, the EROD assay was performed after 24, 48, 72 or 96 h.

Inhibition of prostate cancer cell growth by SAhRMs

Results of preliminary studies presented in this grant proposal showed that TCDD inhibited growth of prostate cancer cells. Another objective of Task 1 was to further investigate the effects of SAhRMs on growth of prostate cancer cells, and the results indicate that DIM inhibits growth of PC3 cells in serum-free or 1% serum-

containing medium at concentrations as low as 0.1 μM DIM (Fig. 4). Similar results were obtained for both DIM and 6-methyl-1,3,8-trichlorodibenzofuran (6-MCDF) in 22RV1 cells (Fig. 5) and demonstrate that both classes of SAhRMs inhibit growth of prostate cancer cells.

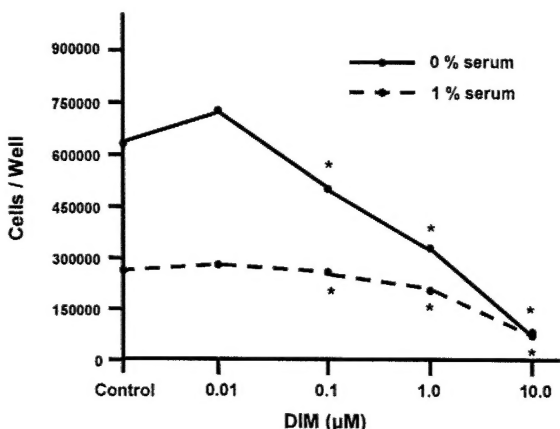


Figure 4. Inhibition of PC3 prostate cancer cell growth by DIM. Cells (10^5) were seeded in 6-well plates and treated with different concentrations of DIM for 6 days. Significant ($p < 0.05$) inhibition of cell growth is indicated by an asterisk and results are presented at means \pm SE for at least three replicate determinations.

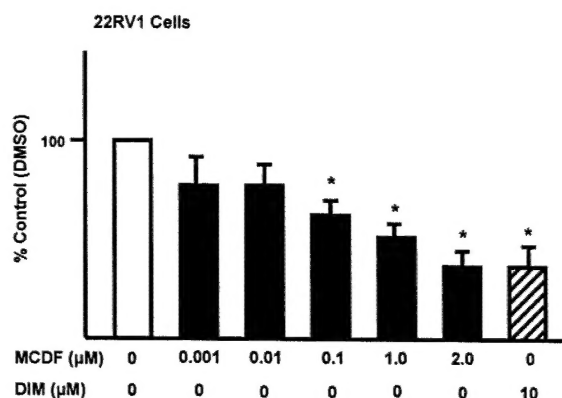


Figure 5. Inhibition of 22RV1 cell growth by 6-MCDF and DIM. Cells were essentially treated as described for PC3 cells (Fig. 4) and significant ($p < 0.05$) induction is indicated by an asterisk.

Effects of TCDD, dihydrotestosterone (DHT) and E2 on AR levels

The AR is expressed in 22RV1 prostate cancer cells, and we have investigated the time-dependent effects of DHT, 17β -estradiol (E2), TCDD, E2 plus TCDD, and DHT plus TCDD on AR protein expression in this cell line (Task 2). Ligands for several receptors initiate degradation of their cognate receptors (37-46); for example, estrogens, retinoids and progestins trigger proteasome-dependent ER, RXR/RAR and PR protein downregulation. One report showed that androgens do not induce downregulation of AR protein in LNCaP cells (47); however, in untreated cells, the proteasome inhibitor MG132 enhanced AR protein levels in the same cell line. TCDD

and SAhRMs induce proteasome-dependent degradation of the AhR and ER α in breast cancer cells (48), and we therefore investigated inhibitory AhR-AR crosstalk on AR protein expression. The results in Figure 6 demonstrate that 10 nM DHT induces a time-dependent > 3.5-fold increase in AR protein expression over a treatment period of 24 h, whereas 10 nM E2 or TCDD alone (or in combination) had no effect on AR protein levels. In 22RV1 cells cotreated with TCDD plus DHT, the increased expression observed with DHT alone was repressed by TCDD. Similar results were observed in LNCaP cells (data not shown), and current studies are focused on the role of this response in mediating inhibitory AhR-AR crosstalk in prostate cancer cells.

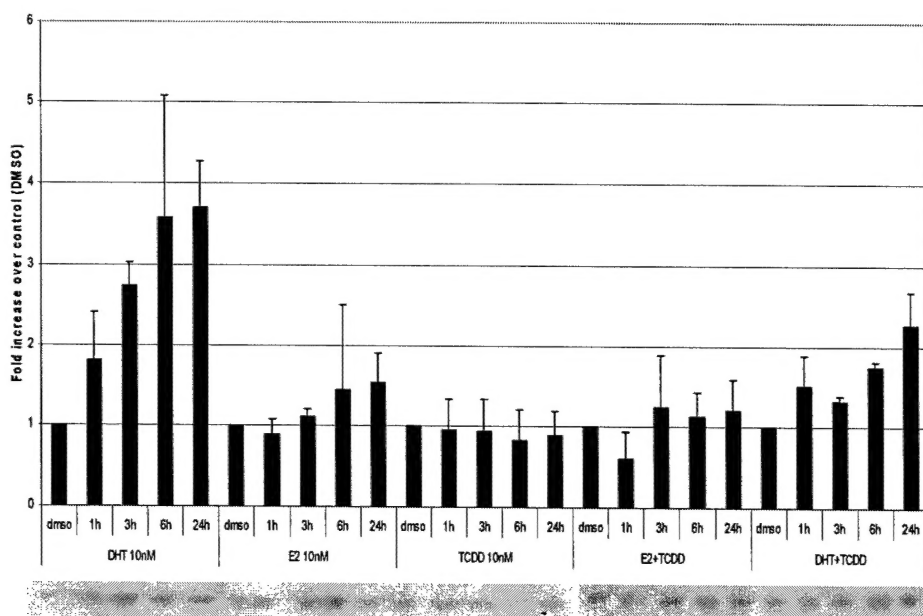


Figure 6. Effects of DHT, E2, TCDD and their combination on AR protein expression on 22RV1 cells. Results are expressed as means \pm SD for at least three replicate determinations.

KEY RESEARCH ACCOMPLISHMENTS

- 22RV1 prostate cancer cells have been identified as Ah-responsive.
- PC3 prostate cancer cells are also Ah-responsive but this is dependent on a lag time for activation of CYP1A1-dependent activity.
- SAhRMs inhibit growth of both 22RV1 and PC3 prostate cancer cells.
- DHT induces upregulation of AR protein in 22RV1 and LNCaP cells.
- E2 and TCDD do not affect AR protein expression in 22RV1 cells.
- TCDD partially blocks DHT-dependent upregulation of AR protein in 22RV1 cells.

REPORTABLE OUTCOMES

Safe, S. and McDougal, A. Mechanism of action and development of selective aryl hydrocarbon receptor modulators for treatment of hormone-dependent cancers. *Int. J. Oncol.* 20:1123-1128, 2002.

Morrow, D., McDougal, A. and Safe, S. Comparative aryl hydrocarbon receptor-hormone receptor crosstalk in breast and prostate cancer cells. Society of Toxicology Annual Meeting, Nashville, TN. March, 2002.

CONCLUSIONS

Initial studies have demonstrated that PC3, 22RV1 and LNCaP prostate cancer cells are Ah-responsive, and SAhRMs inhibit growth of these cells. TCDD inhibits DHT-induced AR protein expression in these cells, and the role of this inhibitory AhR-AR interaction will be further investigated in the proposed studies. Future work will focus on

critical genes/proteins associated with growth of prostate cancer cells and determine those that are specifically targeted for inactivation by the AhR.

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APPENDIX

1. Safe, S. and McDougal, A. Mechanism of action and development of selective aryl hydrocarbon receptor modulators for treatment of hormone-dependent cancers. *Int. J. Oncol.* 20:1123-1128, 2002.
2. Morrow, D., McDougal, A. and Safe, S. Comparative aryl hydrocarbon receptor-hormone receptor crosstalk in breast and prostate cancer cells. Society of Toxicology Annual Meeting, Nashville, TN. March, 2002.

Mechanism of action and development of selective aryl hydrocarbon receptor modulators for treatment of hormone-dependent cancers (Review)

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Abstract. Ligand-activated receptors are extensively used as targets for developing tissue-selective drugs for treatment of multiple diseases including cancers. The aryl hydrocarbon receptor (AhR) is a basic helix-loop-helix transcription factor that binds both synthetic chemicals such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and naturally-occurring phytochemicals, sterols and heme breakdown products. The high affinity ligand TCDD induces several AhR-mediated changes in gene expression, tissue/species-specific toxicities, and both tumorigenic and anticarcinogenic responses including inhibition of estrogen-dependent mammary and uterine tumor formation and growth. Research in this laboratory has demonstrated that TCDD inhibits E2-induced responses in the rodent uterus and mammary tumors (growth inhibition) and in breast and endometrial cancer cell lines through complex inhibitory AhR-estrogen receptor (ER) crosstalk. 6-Alkyl-1,3,8-trichlorodibenzofurans and substituted diindolylmethanes represent two structural classes of selective AhR modulators (SAhRMs). These compounds are relatively non-toxic and inhibit ER-positive and ER-negative mammary tumor growth, and synergize with tamoxifen to inhibit breast cancer growth and block tamoxifen-induced estrogenic activity in the uterus. Preliminary studies also indicate that SAhRMs inhibit prostate cancer cell growth, and there is evidence for inhibitory AhR-androgen receptor crosstalk. SAhRMs represent a novel class of drugs for treatment of hormone-dependent cancers, and combined therapies of SAhRMs with tamoxifen and other selective ER modulators (SERMs) provides a new approach for treating women with breast cancer.

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8. Summary

1. Introduction

The aryl hydrocarbon receptor (AhR) is a member of the basic helix-loop-helix family of nuclear transcription factors, and this receptor was initially identified by its high affinity binding to the environmental toxicant, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (1,2). TCDD and structurally-related halogenated aromatics modulate expression of multiple genes which play a role in the species-, sex- and age-specific toxic, genotoxic and anticarcinogenic responses associated with exposure of laboratory animals to these compounds (2-6). The endogenous ligand for the AhR is unknown; however, several reports have now demonstrated that this receptor binds structurally-diverse synthetic chemicals as well as aromatic amines in cooked foods, phytochemicals including indole-3-carbinol (I3C) and related indole-derived compounds, carotenoids, flavonoids, steroidal compounds, and bilirubin (Fig. 1) (7-14). Interestingly, steroid hormone receptors and other ligand-activated nuclear receptors also bind different structural classes of chemicals and many of these receptors are targets for developing drugs that selectively ameliorate one or more receptor-mediated responses. For example, selective estrogen receptor (ER) modulators have been developed as both tissue-specific ER agonists and antagonists for treating breast cancer and various postmenopausal symptoms in women (15). Since the ligand-activated AhR modulates diverse genes/responses, this receptor is an excellent target for drug development. For example, TCDD inhibits spontaneous 17 β -estradiol (E2)-induced mammary and uterine tumor formation in Sprague-Dawley rats suggesting that TCDD exhibits antiestrogenic activity. Research in our

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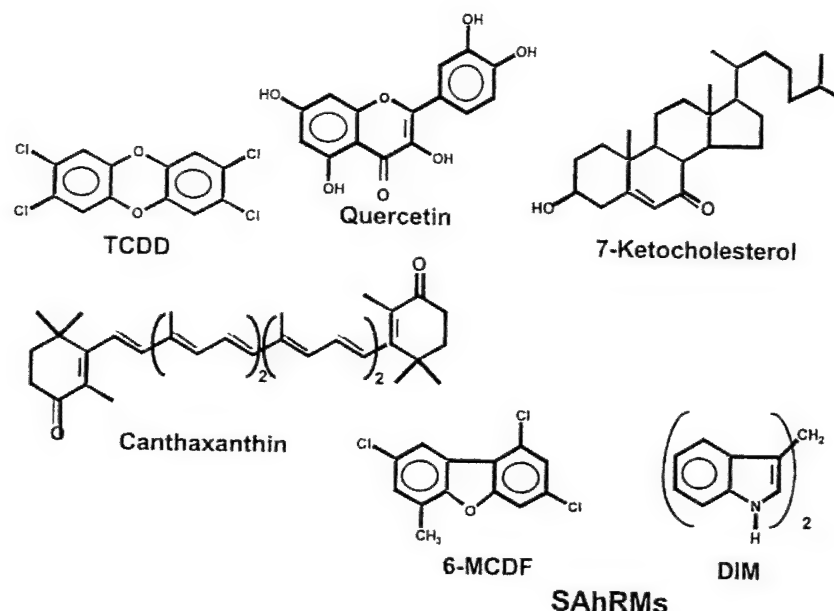


Figure 1. Structurally diverse compounds that bind the Ah receptor including the SAhRMs 6-MCDF and DIM.

laboratory has focused on studying the mechanisms of inhibitory AhR-ER crosstalk (3,16-18) and developing selective AhR modulators (SAhRMs) for treating breast and endometrial cancers (19,20).

2. Inhibitory AhR-ER α crosstalk: *in vivo*

The antiestrogenic/antitumorigenic activity of TCDD observed in female Sprague-Dawley rats stimulated *in vivo* and *in vitro* studies to determine the specificity of this response (reviewed in refs. 13,16-20). The immature and/or ovariectomized female rat and mouse uterus has been used as a model, and TCDD inhibited several E2-induced uterine responses including progesterone receptor (PR) binding, uterine wet weight, peroxidase activity, *c-fos* and epidermal growth factor receptor (EGFR) mRNA levels, and EGFR binding. Similar results were obtained for the growth of E2-dependent mammary tumors in carcinogen-induced Sprague-Dawley rats and athymic nude mice bearing breast cancer cell xenografts. Recent studies (21) also show that women accidentally exposed to TCDD in Seveso, Italy in 1976 exhibit decreased rates of breast and endometrial cancer, and these observations in humans parallel the effects of TCDD in rodents.

3. Inhibitory AhR-ER α crosstalk: *in vitro*

The interactions of the AhR and ER signaling pathways have been investigated in several ER-positive breast and endometrial cancer cell lines, and these include MCF7, ZR-75 and T47D breast cancer cell lines and Ishikawa, HEC1A and ECC-1 endometrial cancer cells. All of these cell lines express the AhR, and AhR agonists such as TCDD induce CYP1A1 gene expression, a highly characteristic Ah-responsive gene in cell

culture and animal models. In addition, TCDD and related compounds also inhibited E2-induced breast and endometrial cancer cell proliferation (22-25). Subsequent studies have demonstrated that AhR agonists inhibit several E2-induced responses at the gene, protein and reporter gene level using constructs containing E2-responsive gene promoter inserts. For example, in MCF-7 human breast cancer cells, TCDD inhibits E2-induced PR, pS2, cathepsin D mRNA and protein levels, *c-fos* and prolactin mRNA levels, cyclin D1 protein, retinoblastoma (Rb) protein phosphorylation, glucose metabolism, and plasminogen activator activity. A major pathway for AhR-mediated inhibition of E2-induced MCF-7 cell proliferation is linked to the selective inhibition of critical E2-induced cell cycle regulatory proteins such as cyclin D1, Rb phosphorylation and E2F1 (Fig. 2), and these inhibitory responses block E2-induced G₁→S phase cell cycle progression (26).

Inhibitory AhR-ER crosstalk is observed not only in breast cancer cells, but also in E2-responsive endometrial and ovarian cancer cells where TCDD inhibits E2-induced cell proliferation (24,25,27). The mechanisms associated with the effects of AhR agonists on hormone-induced cell proliferation have primarily been investigated in breast cancer cell lines (see below); however, it is likely that interactions between AhR-ER signaling pathways are comparable in breast, endometrial and ovarian cell lines.

4. Mechanisms of AhR-ER crosstalk

Results of initial studies in this laboratory showed that TCDD inhibited E2-induced expression of multiple genes and similar results were observed in transient transfection studies using constructs containing E2-responsive gene promoter inserts. These results suggested that the ligand-bound AhR disrupted

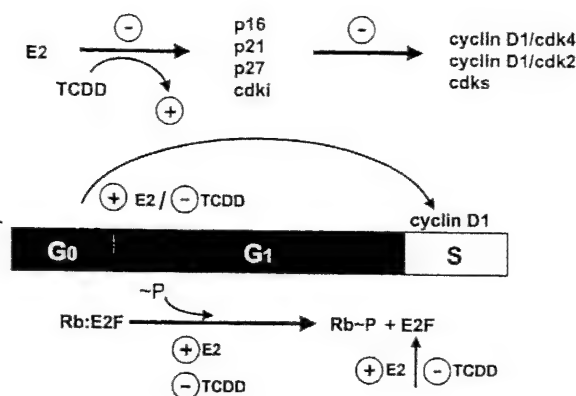


Figure 2. Interactions of E2 and TCDD on cell cycle progression in MCF-7 human breast cancer cells (26).

a promoter- and E2-dependent transcriptionally-active complex. This type of inhibitory crosstalk could occur via several pathways including AhR-dependent induction or inhibition of a critical factor involved in hormone-induced transactivation, direct interaction of the AhR with critical *trans*-acting factors or associated proteins, and interaction of the AhR with critical *cis*-acting elements (Fig. 3). Analysis of the E2-responsive cathepsin D, *c-fos*, pS2 and heat shock protein 27 gene promoters have identified pentanucleotide GCGTG sequences which are required for inhibitory AhR-ER crosstalk (28-32), and these motifs weakly bind the AhR complex and correspond to the core of a dioxin response element (DRE). Inhibitory DREs (iDRE) are strategically located within gene promoters and block formation of a transcriptionally-active complex. For example, binding of the AhR complex to the upstream iDRE in the cathepsin D gene promoter (-175 to -181) disrupts formation of the ER/Sp1 complex which is also formed in the same region of the promoter (-199 to -165). Results of more recent studies demonstrate that several constructs containing E2-responsive gene promoter (e.g. retinoic acid receptor α 1) inserts are also inhibited by AhR agonists in transient transfection studies, and these promoters do not contain functional iDREs. Currently, we are investigating other mechanisms including the role of AhR-activated proteasome-dependent degradation of the ER (33) and sequestration of the ER through direct AhR-ER interactions.

5. Selective AhR modulators (SAhRMs) for treatment of ER-positive breast cancer

The environmental toxicant TCDD has been routinely used as a prototype for investigating AhR-mediated responses including inhibitory AhR-ER interactions in the rodent uterus and mammary tumors and in breast/endometrial cancer cells. Alternate substituted 6-alkyl-1,3,8-trichlorodibenzofurans were initially characterized as AhR antagonists which exhibited low toxicity, and in combination with TCDD, one of these analogs [6-methyl-1,3,8-trichlorodibenzofuran (6-MCDF)] (Fig. 1) inhibited TCDD-induced CYP1A1 gene

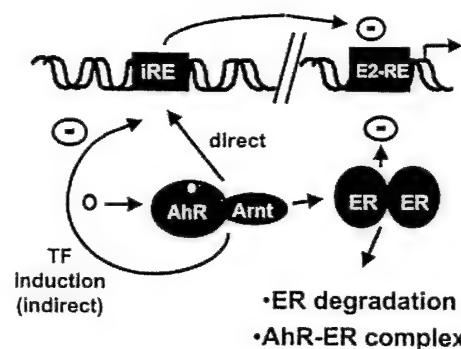


Figure 3. Inhibitory AhR-ER crosstalk. Inhibitory responses are gene-specific and may involve direct interactions with iDREs (28-32), proteasome-dependent degradation of ER (33), or induction of inhibitory transcription factors (TFs).

expression, immunotoxicity, hepatic porphyria, and cleft palate in mice (34-37). However, 6-MCDF and related compounds were agonists for inhibitory AhR-ER crosstalk in both *in vitro* and *in vivo* models (38-41). For example, 6-MCDF inhibits carcinogen-induced mammary tumor growth in female Sprague-Dawley at doses as low as 50 μ g/kg per day (42,43). Moreover, in ovariectomized female rats of a comparable age, 6-MCDF inhibited tamoxifen-induced estrogenic responses in the uterus (e.g. peroxidase activity, progesterone receptor binding) but did not affect the ER agonist effects of tamoxifen on bone growth (43). These results, coupled with the observed inhibitory AhR-ER crosstalk in endometrial cancer cells suggest that combined therapy with SAhRMs, such as 6-MCDF plus tamoxifen, will be highly effective for treating mammary cancer and also protecting against tamoxifen-induced estrogenic responses in the uterus. This latter interaction is important since long-term treatment with tamoxifen is associated with an increased incidence of endometrial cancer (44). We have also investigated the AhR agonist activities of diindolylmethane (DIM) (Fig. 1) and a series of dihalo- and dialkylDIM analogs (45-47). These compounds bind the AhR and exhibit some of the agonist/antagonist activities observed for 6-MCDF. Moreover, in rodent models for mammary carcinogenesis, many of the DIM compounds were potent inhibitors of mammary tumor growth.

6. SAhRMs for treatment of ER-negative breast cancer

The AhR is expressed in ER-positive and -negative breast cancer cell lines and in human mammary tumors; however, initial studies indicated that the AhR was not functional in ER-negative cell lines and the diagnostic induction of CYP1A1-dependent activity by TCDD was not observed (48,49). This failure to observe induction could be overcome by transient overexpression of ER α (50,51), and a recent study suggested that Ah non-responsiveness in ER-negative MDA-MB-231 cells may be linked to overexpression of heat shock protein 90 which sequesters and inactivates the AhR (52). ER-negative MDA-MB-468 express a functional AhR

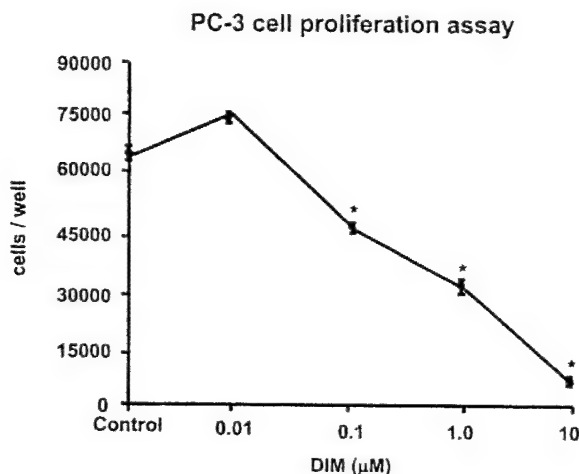


Figure 4. Inhibition of PC3 prostate cancer cell growth by different concentrations of DIM.

and TCDD induces CYP1A1 gene expression; moreover, both TCDD and 6-MCDF inhibit MDA-MB-468 cell growth through induction of transforming growth factor α which is growth inhibitory in this cell line (53). Results of ongoing studies also indicate that 6-MCDF inhibits tumor growth in athymic nude mice bearing MCF-7 or MDA-MB-468 cell xenografts. In addition, a more extensive survey of ER-negative breast cancer cells shows that several of these cell lines, including MDA-MB-453, MDA-MB-435, HCC-38 and BT-20 cells, express a functional AhR (i.e. CYP1A1 inducibility by TCDD) and 6-MCDF inhibits cell proliferation. Current studies are further characterizing the growth inhibitory and antitumorigenic activity of 6-MCDF and related SAHRMs using ER-negative breast cancer cells and thereby expanding the potential therapeutic applications of SAHRMs for treating breast cancer.

7. Potential applications of SAHRMs for treating other cancers

The AhR is expressed in cancer cells derived from tumors from multiple tissues; however, the potential applications of SAHRMs for inhibiting growth of these tumors has not been extensively investigated. Research in this laboratory has demonstrated that TCDD and/or 6-MCDF inhibit E2-induced proliferation of E2-responsive PE04 ovarian and Ishikawa/ECC1 endometrial cancer cell lines (24,25,27). Smoking is known to be protective for development of endometrial cancer in women and benzo[a]pyrene, an AhR agonist that is a component of cigarette smoke and other combustion products also inhibits E2-induced proliferation of Ishikawa endometrial cancer cells (25,54,55). Recent studies show that AhR agonists also block androgen receptor (AR) signaling including testosterone-induced prostate-specific antigen (protein and mRNA) (56,57). We have also investigated inhibitory AhR-AR interactions in prostate cancer cells and the results in Fig. 4 demonstrate that DIM inhibits proliferation of PC-3 prostate cancer cells maintained in 0

and 1% serum. These results suggest that SAHRMs may also be useful for inhibiting prostate and possibly other cancers, and the applications and mechanisms of action of these compounds are currently being investigated.

8. Summary

Ligand-activated receptors are ideal targets for developing tissue-selective modulators for treating different diseases. The AhR is widely expressed in mammalian tissues and tumors, and it is clear from studies on TCDD that multiple genes/responses are mediated through the AhR, and these include inhibition or enhancement of immune responses, reproductive toxicity, a wasting syndrome, carcinogenic and anticarcinogenic responses, proteasome activation, and tissue-specific up- or downregulation of several genes. Our research has focused on development of tissue-selective SAHRMs for treatment of mammary cancer and it is possible that SAHRMs may also inhibit growth of tumors in other tissues, and these are currently being investigated.

Acknowledgements

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COMPARATIVE ARYL HYDROCARBON RECEPTOR-HORMONE RECEPTOR CROSSTALK IN BREAST AND PROSTATE CANCER CELLS. D Morrow, A McDougal and S Safe. Department of Veterinary Physiology & Pharmacology, Texas A&M University, College Station, TX, USA.

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is a ligand for the aryl hydrocarbon receptor (AhR) and inhibits growth of both breast (T47D) and prostate (LNCaP and 22RV1) cancer cells in culture. One mechanism for TCDD-induced inhibitory activity in breast cancer cells involves activation of proteasome-dependent degradation of estrogen receptor α (ER α). This study investigated the comparative effects of TCDD and steroid hormones on receptor proteins in breast and prostate cancer cells. T47D, LNCaP and 22RV1 cells express the androgen receptor (AR) and, after treatment with 10 nM dihydrotestosterone (DHT) for 24 h, there was a significant 4- to 6-fold upregulation of immunoreactive AR protein, and this increase was observed within 1 to 3 h after treatment in all three cell lines. In contrast, 17 β -estradiol (E2) decreased AR levels in T47D cells, whereas in prostate cancer cells, AR levels were slightly elevated by E2. TCDD induces proteasome-dependent degradation of ER α in breast cancer cells; however, after treatment with 10 nM TCDD for up to 24 h, only minimal changes in immunoreactive AR protein were observed in T47D breast and 22RV1 prostate cells. Combined treatment with DHT plus TCDD resulted in some decreases in AR protein in 22RV1 cells (compared to treatment with DHT alone), whereas TCDD did not alter upregulation of AR protein by DHT in T47D cells. Thus, the effects of TCDD on AR and other hormone receptors in prostate and breast cancer cells are dependent on cell context, and current studies are focused on the mechanisms of AhR-hormone receptor crosstalk in both breast and prostate cancer cell lines (Supported by DOD-USAMRMC 17-02-1-0147 and NIH ES09106).

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Topic #s	41	33	18
Keywords	Hormone receptors	TCDD	crosstalk